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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,286	10/16/2001	John Fruehauf	97,150-C	8043

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EXAMINER	
HUMPHREY, DAVID HAROLD	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,286	FRUEHAUF, JOHN	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *11-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/10/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, claims 1-10, in the reply filed on September 29, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 11-20 are withdrawn as being to a non-elected invention.

Claims 1-10 are examined on the merits.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-7 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a prognosis of disease course in a breast cancer or prostate cancer patient, does not reasonably provide enablement for a method for making a prognosis of disease in melanoma or any other cancer patient other than breast or prostate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'. " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claims broadly recite a method of making a prognosis of the disease course in a human cancer patient. Thus, claims 1-7 encompass any and all types of cancer in addition to the limitation of melanoma recited in claim 10. The method comprises the steps of determining the level of nuclear localization of p53; determining the level of thrombospondin-1 and determining the extent of microvascularization, wherein the prognosis is made when p53 nuclear localization and extent of microvascularization is greater than in a non-invasive, non-metastatic tumor sample and wherein the level of thrombospondin-1 is less than that in a non-invasive, non-metastatic tumor sample. The method further comprises preparing an index comprising the results of the

determination of p53 nuclear localization, thrombospondin-1 expression, and the extent of microvascularization in the tumor sample.

The claims broadly encompass any method for measuring the extent of vascularization.

As evidenced by Hedge et al (Arch Otolaryngol Neck Head Surg Vol 124: 80-85, January 1998; cited in Applicant's IDS), "methods for the determination of MVD [micro vessel density] vary considerably among investigators" (pages 83-84, bridging paragraph). Hedge et al. teach that "both direct counts and subjective vascularity grading scales have been used" (pages 83-84, bridging paragraph). Hedge et al. teach that computer image analysis methods prove unsatisfactory and that it is necessary to evaluate significant vessel morphological characteristics and caliber to distinguish neovascularization (page 84, left column, first full paragraph). These qualitative distinctions require a trained observer" (page 84, first full paragraph). Hedge et al summarize that "because of the complexity of measuring angiogenic activity and the complexity of the effect of tumor angiogenesis to therapy, further study is warranted" (page 84, final paragraph).

Similarly, Gasparini et al. (J. Clinical Oncology 12(3):454-466 (1994)) teach that discrepancies in MVD results suggest possible methodological problems. In particular, Gasparini et al. teach that "significance of the MVD decreases when the field size is smaller than 0.19mm2" (page 464, left column, lines 19 and 20). Gasparini et al. stress that the published protocols should be followed carefully and that experience is needed

to highlight microvessels, recognize countable microvessels and select the appropriate hot spots" (page 464, bottom left column).

Salvesen et al. (Int. J. Cancer 84:539-543 (1999); cited in Applicant's IDS) teach that the "formation of new vessels represents a complex multistep process which might be stimulated or inhibited by several different factors" (page 539, left column, second paragraph).

One skilled in the art would reasonably conclude, from the teachings of Hedge et al., Gasparini et al., and Salvesen et al. that different results will be obtained using the various different methods of measuring the complex process of MVD, only some of which would reasonably correlate to the prognosis determination claimed. However, the claims broadly encompass using any method to measure the extent of microvascularization.

The claims broadly recite a method for prognosing any cancer or any additional neoplastic disease.

Hedge et al. teach that some tumors do not require angiogenesis and that gliomatosis grow as sheets of cells between membranes without the requirement of neovascularization (page 84, third full paragraph, bridging the left and right columns). Additionally, Hedge et al. teach that they were unable to find any correlation between MVD and response to therapy or survival in head and neck cancers (page 84, right column, second full paragraph). Moreover, Hedge et al. teach that those skilled in the art are in conflict as to whether a high level of vascularity is an indicator of aggressive tumor behavior in breast, bladder, and prostate cancers or a high level of vascularity is

an indicator of better response to radiotherapy and chemotherapy (page 80, second full paragraph).

Similarly, Oshika et al. (Clinical Cancer Research 4: 1785-1788 (1998); cited in Applicant's IDS) teach that they "found no significant relationship between TSP-1 gene expression and clinical or pathological features of non-small cell lung cancer" (page 1787, right column, second full paragraph).

Salvesen et al. teach that "in vitro results on melanoma cells show[ing] that TSP-1 inhibited tumour cell proliferation" (page 542, third full paragraph). Additionally, Salvesen et al. teach that "studies of non-small cell lung cancer, colon cancer and breast cancer do not show any significant association between TSP-1 expression and prognostic factors or prognosis. Our results (on endometrial cancer) are in line with these latter studies" (page 542, right column, bottom of third full paragraph).

The specification enables only the methods using breast cancer samples (Example 1, pages 8-14), and prostate cancer (Example 3, pages 16 and 17) with the measurement of the three markers using the methods recited in the examples, including the methods of measuring for the extent of microvascularization, the methods of weighing the results, making the index, and determining the prognostic results. The specification has not provided adequate enablement for the full scope of the claims including melanoma and any other types of cancer. The art teaches the complexity of MVD measurements, the complexity of the process of angiogenesis and the discrepancy between using the TSP-1 as a marker for the full scope of the claims as recited. In view of the lack of guidance and working examples, the unpredictability of

the art, it would require one of ordinary skill in the art undue experimentation to practice the claimed invention.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 9 and 10 of U.S. Patent No. 6,303,324 (cited in Applicant's IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and Patent '324 encompass a method making a prognosis of disease course in a human

cancer patient by determining the nuclear localization of p53 protein, the level of thrombospondin-1 expression, and the extent of microvascularization.

The claims recite a diagnostic method to determine disease progression in a human cancer patient by obtaining a sample of the tumor, determining the nuclear localization of p53, the level of thrombospondin-1 expression, and the extent of microvascularization in the tumor sample as compared to a non-invasive, non-metastatic tumor sample. A higher level of nuclear localization of p53, a lower expression of thrombospondin-1, and a greater extent of microvascularization in comparison to the non-invasive, non-metastatic control sample, are predictive factors for the likelihood of further neoplastic disease, see claim 1. Patent '324 also teaches the localization of p53 protein in the tumor sample is about twofold to tenfold greater than the nuclear localizationof p53 protein in the non-invasive, non-metastatic sample, see claims 2, 5, and 6. Similarly, Patent '324 teaches the thrombospondin-1 expression in the tumor sample is about twofold to tenfold less than the level of thrombospondin-1 expression in the non-invasive, non-metastatic sample, see claims 3, 5, and 6. Patent '324 also teaches that the extent of microvascularization in the tumor sample is from twofold to tenfold greater than the extent of microvascularization in the non-invasive, non-metastatic tumor sample, see claims 4, 5, and 6. Patent '324 teaches that the level of p53, the level of thrombospondin-1 expression and the extent of microvascularization are determined by immunohistochemical staining, see claim 7. In addition, Patent '324 teaches the preparation of a prognostic index comprising the results of the determination of the levels of nuclear localization of p53, thrombospondin-1 expression,

and the extent of microvascularization in the tumor sample, see claim 8. Patent '324 teaches the method wherein the cancer is breast cancer and prostate cancer, see claims 9 and 10.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Humphrey, Ph.D.

November 15, 2005

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER